AF/1617

PATENT

Attorney Docket No. **OPHD-06331**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCE

In re Application of:	John A. Kink		
Serial No.:	09/832,233	Group No.:	1617
Filed:	04/10/01	Examiner:	Sharareh, S.
Entitled:	**Prevention and Treatment of Necrotizing Enterocolitis**		

APPELLANTS REPLY BRIEF TRANSMITTAL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8(a)(1)(i)(A)

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being deposited with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Dated: July 5, 2005 By: Christopher J. Collins

Sir or Madam:

Enclosed herewith, please find the Appellants Reply Brief in triplicate with respect to the Examiner's Answer mailed May 4, 2005.

The proceedings herein are for a patent application and the provisions of 37 CFR § 1.136 apply, Appellants believe that no extension of term is required. However, this conditional petition is being made to provide for the possibility that Appellants have inadvertently overlooked the need for a petition and fee for extension of time.

The Commissioner is hereby authorized to charge payment of any fees associated with this communication or credit any overpayment to Deposit Account No. **08-1290**. **An originally executed duplicate of this transmittal is enclosed for this purpose.**

Dated: July 5, 2005

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PATENT
Attorney Docket No. **OPHD-06331**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:	John A. Kirk		
Serial No.:	09/832,233	Art Unit:	1617
Filed:	04/10/2001	Examiner:	Sharareh, S.
Entitled:	**Prevention and Treatment of Necrotizing Enterocolitits**		

REPLY TO AN EXAMINER'S ANSWER

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

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Dated: July 5, 2005 By: _____
Christopher J. Collins

Sir/Madam:

On May 4, 2005, the Examiner mailed an Answer to Applicant's Appeal Brief wherein new points of argument are made. Pursuant to 37 CFR 1.193 (b)(1), Applicant hereby provide a Reply Brief wherein the new points of argument are addressed.

Since the Reply Brief is filed within two months of the date of mailing of the Answer, the Reply Brief is timely. Nonetheless if there are any fees required and/or any required Petition for Extension of Time for filing this Reply Brief, they are dealt with in the accompanying **TRANSMITTAL OF REPLY BRIEF**.

ARGUMENT

A. The Examiner Mischaracterizes Eibl II

The Examiner has set forth a new point of argument. The Examiner maintains (for the first time) that Eibl II teaches that "endotoxemia [] has been associated to the pathogenesis of NEC." Examiner's Answer, page 15, lines 10-11. Applicants cannot agree. The text of Eibl II does not mention that endotoxemia is associated with NEC. The link of endotoxemia to NEC is not completed by the teachings Eibl II.

The passage in Eibl II that the Examiner is referring to states "[e]ndotoxins are known to induce IL-6 synthesis, and serum levels of IL-6 are increased in conditions associated with endotoxemia such as thermal injury. The deleterious effects of bacterial toxins are associated with the exaggerated and self-amplifying release of these compounds that cause inflammation, often with lethal results. The lethality of gram-negative bacteremia or endotoxemia has been prevented by the administration of specific, anti-TNF antibodies." Bacteremia occurs when bacteria enter the bloodstream. Endotoxemia is a condition where endotoxin (toxic substances associated with certain bacteria) access the blood stream. These statements suggest anti-TNF antibodies can be useful for the treatment of bacteremia or endotoxemia and not NEC. Eible II does not provided the motivational nexus for an anti-TNF therapy for NEC.

What Eibl I and II do teach is the use of IgA/IgG preparations, which are simply made by fractionating human serum, *i.e.* without any use of antigen. Tables 1 and 2 in Eibl I show that the human serum fraction has some inherent reactivity with pathogens. There is no readily apparent evidence or data (and the Examiner points to none)

supporting the notion that the IgA/IgG prepartions have antibodies to TNF. Indeed, the authors of the reference speculate that the mechanism of action is through pathogen binding. Thus, at best, the antibody preparation of these references is directed to pathogen antigens. By contrast, the present claims say nothing about anti-pathogen antibodies.

B. The Examiner Creates Argument Out Of Mere Possibilities

In the Examiner's Answer, the Examiner suggests that Eibl II teaches "TNF may be involved in the pathogenesis of NEC [necrotizing enterocolitis]" and "endotoxemia may be prevented by administration of specific anti-TNF antibodies" (emphasis added, Examiner's Answer, page 13 line 22-page 14, line 4). The Examiner concludes that this "clearly provides motivation in the art that anti-TNF antibodies can be used for the treatment of NEC" (emphasis added, Examiner's Answer page 14, lines 4-6). Applicant strongly disagrees. The Examiner effectively changes "may" to "must," thereby creating argument out of mere possibilities. It is respectfully submitted that the Examiner - only after reading the Applicant's disclosure - can now go back and try to connect these unrelated statements (i.e., hindsight reconstruction as to what the Eibl II teaches one skilled in the art).

C. The Examiner Overstates The Prior Art Teachings

The Examiner states that Eibl I, Eibl II, Muguruma, and Wolf provide TNF plays an "integral role in the development to NEC". Examiner's Answer Page 6, lines 10-11. The Examiner is overstating the teachings of each of these references. The Examiner

admits that Eibl II teaches "TNF may be involved in the pathogenesis of NEC." (emphasis added, Examiner's Answer, page 13 line 22-23). Wolf states that "[a]n exaggerated release of mediators of inflammation has also been implicated in the pathogenesis. In infants with NEC, plasma levels of inflammatory cytokines like platelet activating factor (PAF) and tumor necrosis factor (TNF) are elevated. (emphasis added, Page 38, first column, first sentence of last paragraph.) In fact, the conclusion of the paragraphs cited by the Examiner to indicate an important role of TNF entitled "Role of TNF-alpha and LPS in necrotizing enterocolitis development" concludes that "[n]ecrosis could not be demonstrated in any of the animals receiving LPS or TNF-alpha alone [without PAF], even at high doses." Page 576, last sentence of second paragraph. If anything, looking at these references collectively, one skill the art would conclude that they teach that TNF does not "play a primary role" in NEC. Thus, the definitive link of TNF to NEC is not completed by the teachings Eibl, Wolf, and Muguruma. It is only after reading the Applicant's disclosure that the Examiner can now go back and try to connect these statements (i.e., hindsight reconstruction as to what the Eibl, Wolf, and Muguruma teaches one skilled in the art).

D. The Examiner's Argument Is Extreme

The Examiner apparently takes the position that Le provides motivation to use anti-TNF antibodies for any and all TNF-associated disease. Looking at the text of Le, the Examiner could argue that Le provides motivation to use anti-TNF antibodies for treating, hepatitis, lupus, AIDS, cancer, and multiple sclerosis. These are all indications provided in Le (with no data). Is the Examiner suggesting such a teaching in Le means

that anti-TNF antibodies could actually cure all these diseases? Col. 33, line 56-Col 35, line 24. Using the Examiner logic, Le motivates and teaches success for the use of anti-TNF antibodies to cure most all diseases known to man. Without data, the treatment of cancer has long been considered by the USPTO to be an incredible claim. It seems to be an extreme position to maintain that Le provides sufficient expectation of success for the treatment NEC when there is no data in Le confirming such an indication. The Examiner instead relies on the fact that anti-TNF worked for some other indications and the statement that "obviousness does not require absolute predictability of success." (Examiner's Answer page 12, lines 5-6).

The Board is reminded of the many cases that say the chemical and biological arts are inherently unpredictable. The Board is also asked to consider whether those skilled in the art at the FDA would take such an extreme position. For example, it is extremely unlikely the FDA would approve a phase 2 Investigational New Drug Application (IND) using anti-TNF antibodies for the treatment of NEC based on Le without animal data indicating that anti-TNF antibodies may be effective in treating the NEC.[1] The Examiner is merely disregarding that one skilled in the art would consider reasonable.

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[1] 21 CFR312.22 FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety. . . .FDA's review of Phases 2 and 3 submissions will also include an assessment of the scientific quality of the clinical investigations and the likelihood that the investigations will yield data capable of meeting statutory standards for marketing approval.
21 CFR312.23. IND content and format. Section (a)(8)(i) Pharmacology and drug disposition. A section describing the **pharmacological effects and mechanism(s) of action of the drug in animals**, and information on the absorption, distribution, metabolism, and excretion of the drug, if known.

E. The Present Invention Is Not Obvious

Sometimes the trick to invention is identifying "unmarked trees." In re Ruschig, 379 F.2d 990, 994-95, 154 USPQ 118, 122 (CCPA 1967). (It is an old custom in the woods to mark trails by making blaze marks on the trees. It is no help in finding a trail . . . to be confronted simply by a large number of unmarked trees. Appellants are pointing to trees. We are looking for blaze marks which single out particular trees.) Le mentions numerous other indications but Le does not mention NEC. The fact that necrotizing enterocolitis was not listed among a numerous list of possible indications suggests that it was not on the radar: necrotizing enterocolitis was the discovery of an "unmarked tree."

We respectfully, submit that looking at the references themselves would not obviously lead one skilled in the art to create the Applicant's invention. Even if the Examiner has established a *prima facie* case of obviousness (which we do not agree), we have sufficiently rebutted by pointing out the weakness in the Examiners cited references as to what they teach, and considering the invention as whole, the invention as encompassed in the currently pending claims satisfies the requirements of 35 U.S.C. Section 103(a).

Dated: July 8, 2005

Respectfully submitted
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